



Gastrointestinal and eating problems in women with Ehlers–Danlos syndromes

Carolina Baeza-Velasco^{1,2,3} · Sonia Lorente^{4,5} · Elisabet Tasa-Vinyals^{6,7} · Sébastien Guillaume^{2,3} · Maria Soledad Mora⁷ · Paola Espinoza⁷

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Abstract

Purpose Ehlers–Danlos syndromes (EDS) are a group of heritable conditions in which abnormal collagen synthesis leads to features such as joint hypermobility, skin abnormalities, and tissue fragility. Gastrointestinal (GI) symptoms are common among those affected. These may negatively impact eating behaviors, leading to weight/nutritional problems. We aimed to compare GI symptoms, disordered eating, and body mass index (BMI) between EDS patients and healthy controls, and to explore the link between these variables in EDS patients.

Method In this cross-sectional study, women with EDS and healthy controls responded to an online survey assessing GI symptoms (heartburn/regurgitations, early satiety, nausea/vomiting, bloating, abdominal pain, dysphagia), food allergies/intolerances, disordered eating, history of eating disorders (ED), and BMI. We performed intergroup comparisons as well as multivariate analyses to explore the associations between disordered eating, GI symptoms, and BMI in the EDS group.

Results Sixty-six women with EDS and 39 healthy controls were included in the study. The EDS patients showed significantly more GI symptoms and food allergies/intolerances, increased prevalence of ED history, higher risk of current ED, and lower BMI than the controls. In the EDS group, the risk for ED was associated with GI symptoms; restricted eating was associated with GI symptoms, food allergies/intolerances, and dysphagia; uncontrolled eating was associated with GI symptoms; and BMI was associated with GI symptoms and food allergies/intolerances.

Discussion Our results are concordant with that of previous reports highlighting the high level of GI problems and disordered eating in women with EDS. In addition, and for the first-time, the association between both is evidenced in this specific population.

Level of evidence III Case-control analytic study.

Keywords Ehlers–Danlos syndrome · Joint hypermobility · Gastrointestinal problems · Disordered eating · Food allergies · BMI

✉ Carolina Baeza-Velasco
carolina.baeza-velasco@u-paris.fr

¹ Laboratoire de Psychopathologie et Processus de Santé, Université de Paris, F-92100 Boulogne-Billancourt, France

² Department of Emergency Psychiatry and Acute Care, CHU Montpellier, Montpellier, France

³ Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France

⁴ Department of Psychobiology and Methodology of Health Science, Universitat Autònoma de Barcelona, Cerdanyola, Barcelona, Spain

⁵ Paediatric Department, Hospital de Terrassa, Consorci Sanitari de Terrassa, CST, Barcelona, Spain

⁶ Department of Psychiatry and Mental Health, Osona Salut Mental. Consorci Hospitalari de Vic, Vic (Barcelona), Catalonia, Spain

⁷ Departament de Psicologia, Unitat d'Avaluació i Intervenció en Imatge Corporal, Clínica i de la Salut, Universitat Autònoma de Barcelona, Barcelona, Spain

Introduction

Ehlers–Danlos syndromes (EDS) are a group of hereditary connective tissue disorders caused by abnormal collagen synthesis. The common features of EDS are joint hypermobility (JH), skin softness and hyperextensibility, and tissue fragility [1, 2]. This fragility is variable and may range from mild to life-threatening. Indeed, EDS are clinically and etiologically heterogeneous, as illustrated by the descriptions of the 14 recognized EDS subtypes [2]. The most common form of EDS is hypermobile EDS (hEDS), which represents 80–90% of all EDS. Currently, hEDS is conceptualized as being the extreme of a continuum [the so-called hypermobility spectrum disorders (HSD)] that ranges from isolated or asymptomatic JH to hEDS, and includes intermediate phenotypes (i.e., symptomatic hypermobility does not fulfill the criteria for hEDS) [3]. The diagnosis for hEDS and HSD is clinical, whereas genetic confirmatory tests are available for the other EDS subtypes. The only currently available treatment for all EDS forms and for HSD is symptomatic.

As collagen is widely distributed throughout the body, people with EDS and HSD may present manifestations in different body systems. Among the extra-articular symptoms, gastrointestinal (GI) disorders are common, especially functional bowel disorders, reflux, and dyspepsia [4, 5]. Recently, Lam et al. [6] compared the prevalence of Rome IV functional GI disorders between EDS/HSD patients and matched controls (603 in each group). They observed that the vast majority of patients (98%) fulfilled the criteria for a GI disorder. This rate was significantly higher than that observed in the control group (47%; $p=0.0001$). In the same vein, studies exploring the presence of generalized JH in patients attending GI clinics (e.g. [7, 8]) have shown that 33–49% of patients with GI problems have undiagnosed generalized JH, while in the general population, the prevalence of this somatic trait is 10–30% [8]. Unfortunately, the pathophysiology of GI manifestations in EDS/HSD has not been elucidated, and there is a lack of treatment strategies for relieving these symptoms, which strongly impact the quality of life of affected individuals [5, 9].

Although multiple studies have confirmed the connection between EDS/HSD and GI problems [5–8, 10, 11], little is known about other correlates of GI symptoms in EDS/HSD patients, such as eating/weight disturbances. Previously, we highlighted, based on clinical observations, that several patients present with eating and weight problems [12]. These are probably related to EDS/HSD comorbidities such as GI symptoms and food allergies [12], which are also frequent in these patients [13]. According to Santonicola et al. [14], abnormal GI function can

induce certain symptoms of disordered eating (e.g., loss of appetite, self-induced vomiting, dysphagia, constipation, bloating). Thus, as GI problems are overrepresented among EDS and HSD patients, this specific population may be particularly vulnerable to altered eating behaviors as well as weight and nutritional problems. These should be early identified to prevent them from eventually worsening the EDS/HSD clinical features [12].

Some available data support the aforementioned observations. Sanjay et al. [15] reported a high proportion of abnormal body mass index (BMI) in children with JH (57.14% underweight, and 16.67% overweight). We have reported a similar finding in a group of patients with hEDS ($n=80$), in which more than half (57.5%) presented a BMI outside normal ranges [16]. Concerning eating disorders (ED), Goh et al. [17] found that JH was significantly more common among people with anorexia nervosa (63%) than in healthy controls (13%). Later, Bulbena-Cabr   et al. [18] reported that youths with JH presented a significantly higher frequency of bulimia and anorexia than youths without JH. Thus, more research is needed to confirm these preliminary findings and to better understand the intersection between GI problems and eating difficulties in EDS patients. For this reason, the objectives of the present study are twofold: (1) to compare the frequency of GI symptoms and eating/weight problems between EDS patients and healthy participants, and (2) to explore the association among the GI symptoms and eating/weight disturbances in EDS patients.

Methods

Design, setting, and participants

This was a cross-sectional study conducted in Spain. The participants were volunteer EDS patients recruited through the Spanish national patient Asociaci  n Nacional del S  ndrome de Ehlers–Danlos e Hiperlaxitud (ANSEDH), and volunteer healthy controls.

All participants were aged 18 years or older, female, native Spanish speakers, and were required to complete the survey. The EDS patients had to declare their diagnosis of this syndrome to be included. The exclusion criteria for the healthy controls were the presence of personal medical records of connective tissue disorders or diseases related to chronic somatic pain, and the presence of JH syndrome according to the self-reported Screening Questionnaire for JH Syndrome (SQCH ≥ 3) [19].

Measures and instruments

The sociodemographic data collected included age, country of residence, marital status, number of children, and

education and work status. The clinical data collected included EDS subtype, age at diagnosis and an onset of symptoms in the case of patients, weight, height, number and presence of food allergies/intolerances (i.e., gluten, dairy, egg, soy, dry fruits, fish, shellfish, and others), and personal and familiar antecedents of obesity and ED (anorexia nervosa, bulimia nervosa, and ED not otherwise specified). BMI classes according to World Health Organization criteria [20] were calculated based on the self-reported height and weight.

The SQCH [19] was used to assess JH syndrome and to exclude healthy participants susceptible to HSD. The questionnaire is composed of seven items, five of which correspond to the 5-point questionnaire for JH developed by Hakim and Grahame [21], plus two extra-articular features (abnormal scarring and easy bruising). A cutoff score ≥ 3 indicates the presence of JH syndrome. This instrument has adequate clinometric properties [19]. Scale reliability in this study, by Cronbach's α coefficient, is 0.84.

The SCOFF [22, 23]—Spanish version [24] was used for ED screening. The acronym SCOFF relates to one of the words in each of the five true–false items composing the English version of the questionnaire, i.e., Sick, Control, One, Fat, Food. The instrument can be administered in less than 1 min, and the items address the core features of ED such as recent and significant weight loss, distorted body image, or whether the person feels that food controls their life. Scoring consists of adding up the number of affirmative (“true”) answers. Respondents scoring ≥ 2 are considered at risk of an ED. The SCOFF total score is also used for comparing the severity of eating problems between different populations (e.g., [25, 26]). The Spanish version has been successfully validated in Spain in a study that corroborated the psychometric properties of the aforementioned cutoff point, which presented 97.7% sensitivity and 94.4% specificity for detecting ED in primary care settings with adult female patients [24]. The Cronbach α coefficient obtained in the present study was moderate but acceptable (0.61).

The Three-Factor Eating Questionnaire (TFEQ) [27]—Spanish version [28] was administered to assess restrictive and uncontrolled eating. This instrument consists of 17 items graded on a 4-point Likert scale; a higher score reflects a greater degree of pathology, plus an extra 18th item graded on an 8-point Likert scale from no restriction at all to totally restrictive eating. Factor analysis in the Spanish validation confirmed a three-factor structure: restricted eating, uncontrolled eating, and emotional eating. For the purposes of the present study, only restricted eating and uncontrolled eating were used. The items inquire about manifestations of restraint (e.g., avoiding eating or storing certain food types at home for fear of growing fat) and uncontrolled eating (e.g., inability to stop eating once started, appetite influenced by the sight

of others eating). In the aforementioned Spanish validation study, the instrument showed good internal consistency, with Cronbach's α coefficient values ranging between 0.75 and 0.87. In the present study, the coefficient was 0.82 and 0.90 for the restricted eating and uncontrolled eating subscales, respectively.

GI symptoms were assessed using the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) [29]—Spanish version [30]. The PAGI-SYM is a 20-item instrument involving six subscales: heartburn/regurgitation, postprandial fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. The items are presented as short sentences succinctly describing the core manifestations of each symptom in everyday life (e.g., feeling totally fed up, regurgitating, not being able to finish a whole meal). Each item is scored on a 6-point Likert scale. A higher score indicates a more severe symptomatology. The Spanish version has been validated with young adults in Spain, and shows good reliability (Cronbach's α coefficient value = 0.87) and convergent validity, and also displays a 6-factor structure that matches the one described by the original authors. In the present study, the Cronbach α coefficient for this scale was 0.96.

Symptoms of dysphagia were assessed with the Swallowing Quality of Life Questionnaire [31–33]—Spanish version [34]. This is a well-known instrument consisting of 44 items divided into 11 domains: 10 focus on the quality of life and one on symptoms. For the purpose of the present study, only the symptoms subscale (SWAS) was used. This subscale is composed of 14 items assessing how often dysphagia symptoms occur (e.g., coughing, choking when eating, gagging, drooling, or problems chewing). Items are scored on 5-point Likert scales: a lower score indicates a more serious symptomatology. An initial Spanish adaptation study has been published and includes the translation and adaptation [34]. The original questionnaire [33] shows good reliability (Cronbach's α coefficient value > 0.79 for all scales) and excellent 2 week test–retest reliability (Pearson's correlation coefficients of 0.60–0.91). In the present study, the Cronbach α coefficient for the symptoms subscale was 0.87.

Procedure

Information on the EDS patients was obtained through ANSEDH, which issued the questionnaires to its members in January 2020. The healthy controls were recruited from the community and from social networking services (e.g., Facebook). Participants accessed one of two versions of an online self-administered survey—patients or healthy controls—during the first semester of 2020.

Statistical analysis

The statistical analyses were carried out with STATA 16.0. We performed a descriptive analysis of the sociodemographic, anthropometric, and clinical variables [frequency, percentage, mean, standard deviation (SD), median, interquartile range]. Inter-group comparisons were conducted using the Student *t* test or the Mann–Whitney *U* test for quantitative variables, or the chi-square test for categorical variables, and the Fisher test when the expected frequencies for the categorical variables were < 5 . The effect size for quantitative variables and categorical variables was reported by the Cohen coefficient (*d*) and the Cramer V (*V*) coefficient, respectively. For clinical and health categorical variables, the number needed to take (NNT), together with the absolute risk reduction (ARR), also termed absolute risk increase (ARI), when the exposed even rate is higher than the unexposed even rate, were calculated based on the Newcombe method 10 by the Stata bcii package [35, 36].

Multiple linear regression and binary logistic regression (backward selection) models were manually performed to examine the relationship among the criterion variables BMI, TFEQ restrictive eating, TFEQ uncontrolled eating, and risk of ED (SCOFF ≥ 2), and the covariates number of allergies, GI disorder symptoms (PAGI-SYM total score), and dysphagia symptoms (SWAS). The analysis was adjusted by age and BMI. The significance level was taken as 0.05 for all statistical tests. Overlap among covariates was examined with bivariate Spearman's correlations and with the variance inflation factor (VIF).

Ethics

This study was conducted according to the principles expressed in the Declaration of Helsinki of 1975, revised in 1983, and considering the Organic Law 15/1999 of December 13 on the Protection of Personal Data. Ethical approval was obtained from the Comissió d'Ètica en l'Experimentació Animal i Humana (CEEAH) of the Autonomous University of Barcelona in September 2019 (Registration number ID CEEAH 4799). All participants gave their written consent at the beginning of the online survey.

Results

A total of 265 participants accessed the online survey: 132 were EDS patients and 133 were healthy controls. Data from 66 (50%) and 59 (44.4%) participants, respectively, could be exploited for this study (Fig. 1). Twenty participants in the control group were excluded because they had SQCH scores ≥ 3 for hypermobility syndrome, suggesting that they might be in the HSD group. Thus, the final

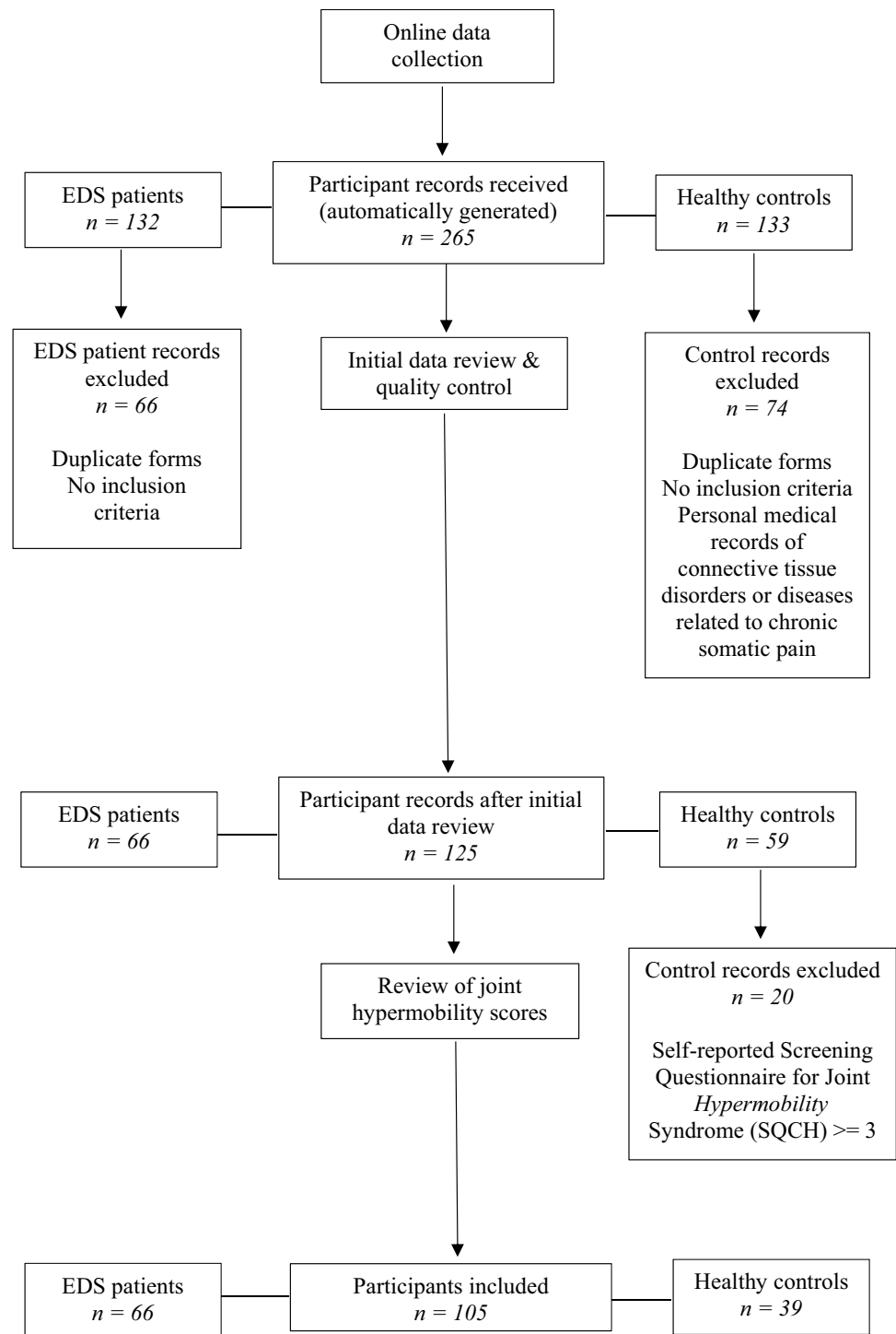
sample was composed of 66 EDS patients and 39 healthy controls (Fig. 1). The distribution of the participants in terms of country of residence is 97.1% from Spain, 0.95% from Argentina, 0.95% from Mexico, and 0.95% from France.

Table 1 shows the sociodemographic and medical history variables. Our findings indicated that there were no significant differences for age, country of residence, marital status, and number of children between the EDS patients and the controls ($p > 0.05$). However, there were significant inter-group differences for education and work status, as a greater proportion of the control group held postgraduate diplomas (33.3% vs. 12.1%) and showed higher rates of employment (74.3% vs. 25.8%). Concerning clinical data, more than half of the EDS patients (51.5%) had been diagnosed with hEDS, 12.1% with classical EDS, 3% with vascular EDS, 15.1% with other forms, and 18.1% declared that they were unaware of their subtype. The mean age of diagnosis was 37.2 years (SD = 11.0), but the mean age at onset of symptoms was 14.1 years (SD = 11.0), representing an average diagnostic delay of 23.8 years (SD = 13.6). Moreover, a significantly greater proportion of the EDS group had self-reported antecedents of ED (36.3% vs. 2.5%; $p < 0.001$; $V = 0.38$), with 33.8% more risk of presenting these antecedents than the control group [95% confidence interval (95% CI) = 18.8; 46.0].

Table 2 shows the comparison of health variables between the EDS patients and the controls. The total score and the subscale scores of the PAGI-SYM, assessing GI symptoms, were significantly higher in the EDS group ($p < 0.001$; $d = 1.68$). In addition, the EDS group had a greater proportion of people with food allergies/intolerances (54.5% vs. 15.3%; $p = 0.001$; $V = 0.38$), as well as a higher number of food allergies/intolerances ($p < 0.001$; $d = 0.64$). Moreover, the EDS group presented significantly lower BMI than the control group ($p = 0.017$; $d = -0.50$). The SCOFF total score (ED symptoms) was also significantly higher in the EDS group ($p < 0.001$; $d = 0.63$). In addition, a greater proportion of people in the EDS group scored ≥ 2 for SCOFF, suggesting they were at risk for an ED (30.3% vs. 12.8%; $p = 0.04$; $V = 0.20$).

Tables 3, 4 show the multivariate analyses performed in the EDS group to explore the factors associated with BMI, restricted eating, uncontrolled eating (TFEQ scores), and risk of an ED (SCOFF score ≥ 2 ; yes/no). The covariates included in all models were GI symptoms (PAGI-SYM total score), number of food allergies/intolerances, and dysphagia symptoms (SWAS score) adjusted by age and BMI. None of the covariates showed collinearity ($r \leq 0.39$; VIF < 10 in all cases).

With BMI as a criterion variable, the multiple regression analyses showed that GI symptoms ($\beta = 0.54$, $p = 0.05$) and number of allergies/intolerances ($\beta = -0.79$, $p = 0.008$) were related to higher BMI. For restricted eating, GI symptoms

Fig. 1 Flowchart of participant selection process

($\beta = 0.11$, $p = 0.003$), dysphagia symptoms ($\beta = 0.17$, $p = 0.014$), number of allergies/intolerances ($\beta = -1.12$, $p = 0.001$), and age ($\beta = 0.13$, $p = 0.02$) were related to higher BMI. For uncontrolled eating, only the GI symptoms scoring ($\beta = 0.11$, $p = 0.008$) was related to higher BMI. Finally, the binary logistic regression indicated that GI symptoms were associated with the group at risk of an ED [odds ratio (OR) = 1.05, $p = 0.007$].

Discussion

This cross-sectional study compared GI symptoms and eating problems between EDS patients and healthy controls, and explored for the first time the association among GI symptoms, eating disturbances, and BMI in EDS patients.

As expected, the EDS patients presented significantly more GI symptoms (heartburn/regurgitation, postprandial

Table 1 Sociodemographic and medical history variables

	No/yes	Healthy controls (<i>n</i> = 39)		EDS patients (<i>n</i> = 66)		<i>p</i>	<i>d</i> (CI 95%)/ <i>V</i>	<i>NNT</i> (CI 95%)
		Mean ± SD/ <i>n</i>	Median (IQR)/ (%)	Mean ± SD/ <i>n</i>	Median (IQR)/ (%)			
Age		40.9 ± 12.8	38.5 (30.5–48.5)	42.7 ± 10.2	42.5 (37.5–47.5)	.414	0.16 (–0.23; 0.56)	
Marital status [†]						.527	0.06	
With partner	16		41.1	23	34.9			
Without partner	23		58.9	43	65.1			
Number of children [§]		0.9 ± 1.2	0 (0–2)	0.9 ± 0.9	1 (0–2)	.966	–0.06 (–0.45; 0.33)	
Educational status [¶]						.035	0.28	
Undergraduate	4		10.3	17	25.8			
Graduate	18		46.1	35	53.0			
Postgraduate	13		33.3	8	12.1			
Others	4		10.3	6	9.1			
Work status ^{††¶}						< .001	–0.50	
Employed	29		74.3	17	25.8			
Unemployed	10		25.7	49	74.2			
Personal medical history								
Obesity						.823	–0.02	–53.6 (–54.4; –52.7)
No	30		76.9	52	78.8			
Yes	9		23.1	14	21.2			
ED (AN, BN and EDNOS)						< .001	0.38	2.9 (2.3; 3.6)
No	38		97.5	42	63.7			
Yes	1		2.5	24	36.3			
Family medical history								
Obesity						.246	0.11	8.9 (8.4; 9.5)
No	28		71.8	40	60.6			
Yes	11		28.2	26	39.4			
ED (AN, BN and EDNOS) [¶]						.078	0.17	7.2 (6.2; 8.1)
No	35		89.7	50	75.8			
Yes	4		10.3	16	24.2			

Comparison between groups

EDS Ehlers-Danlos syndrome, *BMI* Body Mass Index, *TFEQ* Three-Factor Eating Questionnaire, *PAGY* Patient Assessment of Gastrointestinal Disorders Symptom Severity Index, *SWAS* Swallowing Quality of Life Questionnaire—Symptoms scale, *n* sample, % percentage, *SD* standard deviation, *IQR* Interquartile rang, *d* (CI 95%) Cohen's coefficient for effect size, *V* Cramer's V measure of association for categorical variables, *NNT* (95%) Number Needed to Take with confidence interval 95% for clinical categorical variables, *ED* Eating disorders, *AN* anorexia nervosa, *BN* bulimia nervosa, *EDNOS* eating disorder not otherwise specified

[†] With partner Married/living, without partner Single/separated/divorced/widowed

[‡] Employed Working, Unemployed studying/unemployed/retired/ disability/illness/housewife

[§] Mann–Whitney *U* test

[¶] Fisher test.

fullness/early satiety, nausea/vomiting, bloating, lower and upper abdominal pain) and food allergies/intolerances (number and presence) than the controls, with a large to medium effect size. These results are concordant with that of previous reports highlighting the high frequency of GI complaints [5–7, 9–11, 37] and food allergies/intolerances in EDS patients [11, 13].

Although the etiological mechanisms underlying the comorbidity between EDS and GI disorders are poorly understood, it is possible that connective tissue abnormalities lead to alterations in GI tract motility and biomechanics [38]. Autonomic dysfunction is not uncommon in EDS patients and has also been considered a contributor to GI problems [10]. In addition, JH has been associated with

Table 2 Health variables

	No/yes	Healthy controls (<i>n</i> = 39)		EDS patients (<i>n</i> = 66)		<i>p</i>	<i>d</i> (CI 95%) V//NNT ARI (CI 95%)	α
		Mean $\pm$ SD/ <i>n</i>	Median (IQR)/(%)	Mean $\pm$ SD/ <i>n</i>	Median (IQR)/(%)			
SQCH [§]		1 $\pm$ 0.9	1 (0–2)	5.5 $\pm$ 1.4	6 (5–7)	< .001	3.66 (3.02; 4.26)	.84
BMI (kg/m ²) [§]		24.9 $\pm$ 4.9	23.8 (22.2–26.8)	22.7 $\pm$ 3.9	21.6 (20.2–25.3)	.017	–0.50 (–0.90; –0.09)	
BMI status [†]						.509	0.12	
Underweight (< 18.5)		3	7.7	8	12.1			
Normal weight (18.5–29.5)		20	51.3	38	57.6			
Overweight/obesity (> 29.5)		16	41.0	20	30.3			
Food allergies/intolerances						< .001	0.38//2.6 39.2 (20.5; 53.2)	
	No	33	84.7	30	45.5			
	Yes	6	15.3	36	54.5			
Number of food allergies/intolerances [§]		0.3 $\pm$ 0.9	0 (0–0)	1.3 $\pm$ 1.8	1 (0–2)	.001	0.64 (0.23; 1.05)	
PAGI-SYM total score [§]		10.5 $\pm$ 16.2	5 (2–12)	40.6 $\pm$ 18.7	41.5 (24–53)	< .001	1.68 (1.22; 2.14)	.96
Heartburn/regurgitations		2.6 $\pm$ 5.7	0 (0–3)	13.4 $\pm$ 8.6	14 (6–19)	< .001	1.40 (0.96; 1.84)	.93
Postprandial fullness/early satiety		2.9 $\pm$ 3.9	2 (0–4)	7.9 $\pm$ 4.3	8 (4–11)	< .001	1.18 (0.75; 1.60)	.82
Nausea/vomiting		0.7 $\pm$ 2.4	0 (0–0)	3.6 $\pm$ 3.7	3 (0–6)	< .001	0.92 (0.50; 1.33)	.85
Bloating		2.1 $\pm$ 2.7	1 (0–3)	6.4 $\pm$ 2.8	7 (5–8)	< .001	1.58 (1.13; 2.03)	.93
Upper abdominal pain		0.9 $\pm$ 2.2	0 (0–1)	4.4 $\pm$ 2.8	5 (2–6)	< .001	1.31 (0.87; 1.74)	.93
Lower abdominal pain		0.9 $\pm$ 1.9	0 (0–1)	4.7 $\pm$ 2.4	5 (3–6)	< .001	1.65 (1.19; 2.10)	.94
SCOFF [§]		0.4 $\pm$ 0.9	0 (0–0)	1.2 $\pm$ 1.3	1 (0–2)	< .001	0.63 (0.22; 1.03)	.61
Risk of ED (SCOFF $\geq$ 2)						.04	0.20//5.7 17.5 (0.5; 31.4)	
	No	34	87.2	46	69.7			
	Yes	5	12.8	20	30.3			
SWAS ^{††}				52.6 $\pm$ 9.3	54 (48–59)	–		.87
TFEQ								.89
Restricted eating		15.2 $\pm$ 4.2	16 (13–18)	15.4 $\pm$ 5.1	14.5 (12–20)	.815	0.05 (0.34; 0.44)	.82
Uncontrolled eating [§]		17.4 $\pm$ 4.1	17 (13–20)	19.1 $\pm$ 6.4	19.5 (15–23)	.226	0.29 (0.09; 0.69)	.90

Comparison between groups

n sample, % percentage, *SD* standard deviation, *IQR* Interquartile range, α coefficient Internal consistency by Cronbach's alpha, *d* (95%) Cohen's coefficient for effect size, *V* Cramer's V, *NNT* (CI 95%) Number Needed to Take, *ARI* Absolute risk increase with interval confidence 95%, *EDS* Ehlers–Danlos syndrome, *SQCH* Self-reported Screening Questionnaire for Joint Hypermobility Syndrome, *BMI* Body Mass Index, *PAGI-SYM* Patient Assessment of Gastrointestinal Disorders Symptom Severity Index, *ED* Eating disorders, *SCOFF* ED screening, *SWAS* Swallowing Quality of Life Questionnaire—Symptoms scale, *TFEQ* Three-Factor Eating Questionnaire

[§]Mann–Whitney *U* test

^{††}Fisher test

increased interoception (i.e., perception of sensations from inside the body) [39], which in turn is linked to functional GI symptoms [40]. Thus, particularities in body awareness might be involved in the development and maintenance of GI symptoms in these patients.

Furthermore, a higher proportion of the participants with EDS than the controls displayed more current symptoms of

ED (general symptomatology, restricted and uncontrolled eating) and reported a history of ED, with a medium to small effect size. In the same vein, the rate of ED risk according to the SCOFF score was higher in the EDS group, although the effect size was small. It is worth noting that the percentage of people at risk of an ED observed in the EDS group (30.3%) appears very high compared to the figures

Table 3 Results of multiple linear regression models, EDS patients, adjusted by age and BMI

Criterion	Predictors	B	CI 95%	p	F (p)	R ²	Rc ²
BMI	Full model				0.06	0.13	0.08
		Age	0.50 (−0.04; 0.14)	.295			
		PAGI-SYM total score	0.58 (− <.001; 0.12)	.058			
		SWAS	0.00 (−0.11; 0.12)	.943			
		N food allergies/intolerances	−0.79 (−1.37; −0.21)	.008			
		Intercept	19.03 (10.50; 27.56)	<.001			
	Final odel				0.02	0.12	0.09
		PAGI-SYM total score	0.54 (<.001; −0.11)	.050			
		N food allergies/intolerances	−0.79 (−1.36; −0.22)	.008			
		Intercept	21.51 (19.26; 23.75)	<.001			
TFEQ restricted eating	Full model				<0.001	0.29	0.24
		Age	0.12 (0.01; 0.23)	.031			
		BMI	0.21 (−0.09; 0.50)	.166			
		PAGI-SYM total score	0.09 (0.02; 0.16)	.010			
		SWAS	0.17 (0.03; 0.30)	.014			
		N food allergies/intolerances	−0.96 (−1.66; −0.25)	.009			
		Intercept	−5.73 (−17.07; 5.60)	.316			
	Final model				<0.001	0.27	0.23
		Age	0.13 (0.02; 0.23)	.020			
		PAGI-SYM total score	0.11 (0.04; 0.18)	.003			
		N food allergies/intolerances	−1.12 (−1.80; −0.45)	.001			
		SWAS	0.17 (0.04; 0.29)	.014			
		Intercept	−1.79 (−11.70; 8.12)	.719			
TFEQ uncontrolled eating	Full model				0.055	0.14	0.09
		Age	0.06 (−0.10; 0.21)	.466			
		BMI	0.15 (−0.25; 0.56)	.445			
		PAGI-SYM total score	0.67 (−0.33; 0.17)	.184			
		SWAS	−0.13 (−0.31; 0.04)	.145			
		N food allergies/intolerances	0.46 (−0.52; 1.44)	.351			
		Intercept	16.90 (1.14; 32.66)	.036			
	Final model				0.008	0.10	0.09
		PAGI-SYM total score	0.11 (0.03; 0.19)	.008			
		Intercept	14.60 (10.97; 18.21)	<.001			

BMI Body Mass Index, *PAGI-SYM Total* Patient Assessment of Gastrointestinal Disorders Symptom Severity Index total score, *N food allergies/intolerances* Number of food allergies/intolerances, *SWAS* Swallowing Quality of Life Questionnaire—Symptoms scale, *TFEQ* Three-Factor Eating Questionnaire, *B* Coefficient, *CI 95%* Confidence Interval 95%, *p* *p* value, *F(p)* probability of statistic *F*, *R²* *R* squared, *Rc²* Adjusted *R* squared

reported with the same tool in non-clinical young European women (e.g., 13.5% [41]) and Hispanic populations (e.g., 10%; [42]).

Literature on a potential link between EDS and ED is very scarce. This association has been mainly suggested in clinical reports [12, 43, 44]. Some of these reports have highlighted the possibility that disordered eating in these patients could be attributable, or secondary, to EDS symptoms, and a diagnosis of ED might be ruled out when there is no overvaluation of the importance of weight/figure and food, and the presence of this collagen pathology is confirmed [12, 44].

To the best of our knowledge, there is only one published systematic study exploring ED in EDS. Hershenfeld et al. [45] explored anorexia nervosa in 106 EDS patients with different mixed subtypes and reported an ED prevalence of 1.9%. Their study did not include a control group and did not explore other ED subtypes. Unpublished data from a previous study by our group comparing the prevalence of psychiatric disorders in patients with hEDS (*n* = 36) and rheumatoid arthritis (*n* = 40) showed that 16.7% of the hEDS sample reported having an ED at some time during their life, while 2.5% of the rheumatoid arthritis group reported the same (Baeza-Velasco et al. in preparation). Other studies on the

Table 4 Results of binary logistic regression in EDS patients, adjusted by age and BMI

Criterion	Predictors	B	CI 95%	OR CI 95%	<i>p</i>	<i>X</i> ²	<i>R</i> ²
Risk of ED (SCOFF ≥ 2)	Full model					0.028	0.15
	Age	0.01	(−0.05; 0.07)	1.01 (0.95; 1.07)	.756		
	BMI	0.05	(−0.10; 0.20)	1.05 (0.90; 1.22)	.528		
	N food allergies/intolerances	−0.26	(−0.66; 0.15)	0.77 (0.51; 1.15)	.200		
	PAGI-SYM total score	0.06	(0.20; 0.11)	1.06 (1.02; 1.11)	.004		
	SWAS	0.04	(−0.03; 0.12)	1.04 (0.97; 1.12)	.310		
	Intercept	−6.77	(−13.24; −0.30)	0.001 (<.001; 0.74)	.040		
	Final model [†]					.003	0.10
	PAGI-SYM total score	0.05	(0.01; 0.08)	1.05 (1.01; 1.08)	.007		
	Intercept	−2.08	(−4.43; −1.18)	0.06 (0.01; 0.30)	.001		

ED Eating Disorders, SCOFF ED screening binary variable, BMI Body Mass Index, *n* Number, PAGI-SYM Patient Assessment of Gastrointestinal Disorders Symptom Severity Index, SWAS Swallowing Quality of Life Questionnaire—Symptoms scale, *B* coefficient; CI 95% Confidence Interval 95%, *p* *p* value, OR Odds Ratio, *X*² Chi squared, *R*² Pseudo *R* squared

[†]Homer-Lemeshow test for goodness of fit = 6.44 (*p* = 0.59)

hypermobility spectrum showed results in the same direction. Goh et al. [17] reported that JH was significantly more common among patients with anorexia nervosa (63%) than in the relative (34%) and the healthy control groups (13%). In the same vein, Eccles [46] observed a higher proportion of people with ED among psychiatric patients with JH compared to non-hypermobile patients. Finally, Bulbena-Cabr   et al. [18] reported more bulimia and anorexia nervosa in hypermobile youths compared to those without JH.

Interestingly, in the present study, BMI was significantly lower in the EDS group, and the proportion of underweight participants was higher among EDS patients (12.1% vs. 7.6%), although the difference was not statistically significant. In this regard, Sanjay et al. [15] reported a negative correlation between JH score assessed with the Beighton score [47] and BMI in children.

Our results confirm the hypothesis that eating disturbances in EDS are related to GI symptoms [12]. Indeed, multivariate analyses showed that GI symptoms predicted belonging to the group with a SCOFF score that indicated a risk of an ED. In the same vein, restricted eating was associated with GI symptoms, dysphagia, and food allergies/intolerances, and uncontrolled eating was linked to GI symptoms. In this sense, it is well known that people who experience functional GI disorders are more likely to have an ED [48]. Conversely, disordered eating may physiologically alter the GI tract, favoring the onset of GI symptoms [49]. Thus, a vicious circle might be instituted in EDS patients, who are particularly vulnerable with regard to functional GI disorders. That is, altered eating behaviors can appear as a means of avoiding unpleasant visceral sensations, which in turn could worsen GI symptoms and the overall clinical picture of EDS (e.g., underweight or suboptimal nutrition may worsen musculoskeletal symptoms) [12]. In this sense, we observed

that BMI in our EDS sample was also associated with GI symptoms and food allergies/intolerances. This supports the idea that the consequences of GI problems may lead to both behavioral and ponderal consequences.

It is important to mention that in addition to GI problems and food allergies/intolerances, many other signs and physical symptoms common in EDS might negatively impact eating behaviors, such as the fragility of the oral mucosa, hypermobility of the temporomandibular joint, smell/taste alterations, and dental problems, among others [12]. Further studies should take these into account.

This study has several limits. First, the cross-sectional design precludes any inference about the directionality of relationships. In addition, the sample is small, and the participants with EDS were recruited from a patients' association. This implies the self-reported nature of the diagnosis and compromises the generalization of the results. However, the participants were assessed with screening for JH syndrome with the SQCH [19], obtaining a very high score (5.45 out of 7 on average). Although the SQCH is not an instrument for diagnosing EDS, it is a useful screening tool for JH syndrome, which before the publication of the 2017 EDS criteria [1] was considered an entity overlapping with hEDS [50]. Another limitation is that we were unable to access information on the EDS criteria used for each patient, i.e., the Villefranche criteria [51] or 2017 criteria [1]. In hEDS, a condition for which the diagnosis remains clinical, this information is particularly relevant because the 2017 classification is stricter than the preceding one (i.e., the Villefranche criteria [50]). Thus, it is possible that many hEDS patients may not meet the current hEDS criteria but rather the criteria for HSD. Finally, the patient sample is composed of people affected by different EDS subtypes. Although GI symptoms can be present in all subtypes [4], more research is needed

to elucidate the specificities concerning these problems and related eating disturbances according to the EDS variant.

Despite these limitations, the present work supports the clinical observations concerning the implication of GI symptoms in disordered eating behaviors and BMI in people with EDS.

Our findings may aid clinicians' awareness that EDS patients experience a plethora of articular and non-articular symptoms, many of which might have negative implications for eating. These symptoms deserve particular attention to prevent worsening the patient's tissue fragility due to nutritional problems.

No current treatment exists for GI problems in EDS, as for this group of pathologies in general, nutritional advice, supplementation strategies, and patient education are the best management option so far [8]. Moreover, patients with EDS presenting with GI disorders and weight problems should be evaluated by mental health professionals to detect disordered eating behaviors and ED. Conversely, in patients seen in psychiatric/psychological clinical settings who are suspected of or diagnosed with ED and who present JH and musculoskeletal pain, an underlying connective tissue disorder should be considered in the clinical reasoning.

What is already known on this subject?

GI disorders are among the most frequent extra-articular manifestations of EDS. In addition, complaints related to difficulty eating and suspicion of ED are not uncommon among those affected. No systematic study has yet explored the link between GI symptoms and disordered eating in EDS patients.

What does this study add?

This study adds weight to the evidence on the high frequency of GI problems in EDS, and supports the hypothesis that disordered eating is overrepresented in this pathology. In addition, the present study shows a link between GI and eating problems in this population that requires appropriate attention in the clinical management of EDS patients.

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Author contributions CBV and PE designed the study. CBV, PE and ETV collected the data. ETV contributed with data management. SL performed the statistical analysis. CBV drafted the manuscript, and PE, ETV, SL, MSM and SG critically revised the draft for important intellectual content. All authors agreed on the final version.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethics Approval Ethical approval was obtained from the *Comissió d'Ètica en l'Experimentació Animal i Humana* (CEEAH) of the University Autonomous of Barcelona in September 2019 (Registration number ID CEEAH 4799).

Consent to participate All participants gave their written consent at the beginning of the online survey.

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